976,096

PATENT SPECIFICATION 976,096

NO DRAWINGS.

Inventor: —GUSTAV SCHMITZ.

Date of filing Complete Specification : May 23, 1962.

Application Date : Oct. 2, 1961. No. 35555/61.

Complete Specification Published : Nov. 25, 1964.

Index at Acceptance :—A5 B(2S, 2V2, 2Z).

International Classification :—A 61 k.

COMPLETE SPECIFICATION.

Pharmaceutical Compositions.

We, CHEMISCHE WERKE ALBERT, a German Body Corporate of Wiesbaden-Biebrich, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention is concerned with improvements in or relating to pharmaceutical compositions for the treatment of rheumatic diseases.

Extensive literature exists on the treatment of rheumatic diseases with vitamin D, the term "vitamin D" being used herein to mean any one or a mixture of more than one of the members of the vitamin D group. For instance, it is known that "polyarthritis rheumatica chronica", often designated rheumatoid arthritis, has been treated by the administration of large doses of vitamin D, especially vitamin D_2. In 1935, Irving Dreyer and C. I. Reed reported on two year's experience with the treatment of sixty-seven unselected cases, including all types of chronic nonspecific arthritis. ("The Treatment of Arthritis with Massive Doses of Vitamin D". Arch. Phys. Therapy XVI 537). The patients generally received 200,000 U.S.P. units of Vitamin D_2 daily but higher doses up to 500,000 units were administered if no improvement was observed. Occasionally the patients received even larger daily doses up to 1,000,000 units, but the latter was continued for only a few days. These doses were equivalent to 5 mg. up to 25 mg. of vitamin D_2 per day. (1 mg. D_2 = 40,000 I.U.). The treatments were continued daily for weeks and months and the authors reported very good results, improvement being reported in 65% of the cases. At the same time, the authors pointed out the danger of toxic side effects.

Possibly due to the favourable results reported in the above paragraph, other investigators have treated patients suffering from arthritis with vitamin D, usually in daily doses of 5 mg. to 10 mg. The reactions given by the various investigators are not wholly consistent but the investigators are consistent in reporting evidence of toxic side effects when the vitamin D is administered in sufficiently large daily doses to be characteristically therapeutically effective in the treatment of arthritis. Published results may be summarized as follows: —

(1) The works published on vitamin D therapy of arthritis are generally based on a daily administration of a relatively high dose of vitamin D_2, occasionally also D_3, a treatment which was continued for months and years.

(2) The opinions on the therapeutic results obtained vary considerably from little or no effect to very good therapeutic results.

(3) Toxic side effects due to vitamin D therapy were observed in a great number of cases. Very often the toxic side effects made it necessary to discontinue the treatment. Frequently, severe permanent damage did occur.

(4) In spite of quite favourable therapeutic results in some cases, vitamin D therapy was not generally accepted, doubtless due to the danger of toxic side effects.

It has also been proposed to treat polyarthritis rheumatica chronica by intermittently administering high doses (12.5 mg.) of vitamin D_3 or D_2 intramuscularly twice a week. The results were however discouraging, and the author himself states: — "The amounts of vitamin D administered approach the toxic limit. Accordingly this

[*Price* 4*s.* 6*d.*]

treatment is not devoid of danger. On the basis of the series reported this therapy does not seem to be of great benefit".

We have now found a method of administration whereby patients suffering from polyarthritis rheumatica chronica can be treated with therapeutically effective doses of vitamin D whereby toxic side effects are minimised. Surprisingly, it has been found that these results can be achieved by intermittently administering orally even higher daily doses than have heretofore been considered prohibitively toxic. More particularly, it has been found the patient can tolerate between 40 mg. and 100 mg. (1,600,000 to 4,000,000 I.U.) of vitamin D, such as of vitamin D_3, particularly of vitamin D_2, per day provided such a daily dose is administered only every 10 to 18 days. Preferably the doses are in the range between 60 and 80 mg. Generally where the vitamin D is administered in the shorter periods of time of the afore-mentioned ranges, the smaller dosages of the afore-mentioned ranges are applied. In most instances, a typical daily dosage of 70 mg. is administered aproximately every fortnight (14 days) without causing any toxic side effects. It has been found that during the 10 to 18 days waiting period the human organism recovers from the effect of the preceding high dose so that the subsequent like dosages do not lead to any accumulation of side effects for toxic side effects do not occur. The stated method is, of course, not applicable to persons to whom vitamin D is not tolerable, i.e. about 1 to 2 percent of the patients, and who suffer under active tuberculosis, cancer or diseases of the kidneys. Also, the therapy with vitamin D should not be applied simultaneously with that of glucocorticoids.

The present invention is therefore concerned with pharmaceutical preparations suitable for oral administration of the high doses of vitamin D above referred to.

According to the invention we provide pharmaceutical compositions for the treatment of rheumatic diseases which are in solid dosage unit form adapted for oral administration and which comprise vitamin D in association with a pharmaceutical carrier or excipient, each dosage unit containing from 20—150 mg. of vitamin D. Preferred forms of composition are tablets and capsules.

The term "dosage unit form" is used herein in relation to pharmaceutical compositions to designate such compositions in the form of discrete units, each unit being adapted to provide a single therapeutic dose.

Preferably compositions according to the invention are such as contain from 40—100 mg. of vitamin D per dosage unit, a content of from 60—80 mg. of vitamin D being particularly convenient.

As will be seen the present invention provides pharmaceutical compositions particularly suited for the treatment of rheumatic diseases by the method described above. It will be understood that it is most convenient to provide the whole of a daily dose in a single dosage unit; however if desired such dose may be given by means of a portion of a dosage unit such as a half, or (where the dose to be administered is greater than 40 mg.) by two or more dosage units according to the invention. The provision of dosage units according to the invention having a content of at least 20 mg. facilitates the administration of the necessary high dosages.

The preferred member of the vitamin D group for incorporation in the composition according to the invention is vitamin D_2.

The composition according to the invention advantageously comprises the vitamin D in combined form with milk protein, the ratio of vitamin D to milk protein being preferably from 1 : 3 to 1 : 150 by weight, advantageously 1 : 10 to 1 : 100.

Particularly preferred preparations according to the invention contain vitamin D (preferably vitamin D_2) together with vitamin B_1 and preferably also with cholic acid. For example in such a mixture: —

(a) 3.5 parts by weight of vitamin D_2 bound to milk protein may be present besides

(b) 0.5 to 10 parts of vitamin B_1; and

(c) 1 to 10 parts of cholic acid. A particularly satisfactory mixture contains the vitamins D_2 and B_1 and cholic acid in a weight ratio of about 3.5 : 1.5 : 3.

The preparations according to the invention may be formulated in conventional manner. In the preparation of tablets, for example, conventional tabletting procedures may be employed and the active ingredients may be associated with one or more tabletting excipients e.g. starch, lactose, mannitol, hardened gelatine and talc. In the preparation of capsules the active ingredients may be filled into the capsule cases either with or without a diluent. It will be understood that the precise proportion of the various ingredients in the composition according to the invention will be chosen to provide dosage units of convenient size for administration.

The discoveries reported herein are based on the treatment of a large number of patients during a prolonged period with good therapeutic results in over 90% of the cases. Actually, about 96 percent of the patients treated suffering from chronic polyarthritis rheumatica showed good therapeutic improvement. The improvement was evident with patients suffering under degrees I and II of polyarthritis rheumatica chronica, as defined by the American Rheumatism

Association, by a subsidence of the inflammatory symptoms. With these patients the functional improvement is not as obvious since they do not suffer from severe functional disorder. However, the improvement of the function is very impressive with the patients suffering under degrees III and IV of the disease. It happens in relation to the severity of the disease more rapidly than with patients suffering under degrees I and II. Though with these patients suffering under severe degrees III and IV, the anatomic changes which have already occurred are not influenced, the function of the joints is restored and the joints may be moved without aching. The values of the hypotension are reduced to their normal state, other pathologic reactions are diminished and the medical reports become normal again. During the treatment with vitamin D the muscles which show an atrophy due to disuse, increasing the more with the progressive state of the disease of the joints, grow larger in volume and become strengthened, which facts prove that they are used again.

A great many of the patients had previously been treated by other methods and drugs (salicylates, dimethylaminophenazone derivatives, phenylbutazone, gold, steriods; or with physical methods, such as medicated baths, bog-baths, etc., etc.) which treatments generally did not result in stopping the progress of the disease.

The above results have been clinically confirmed by independent investigators.

The significance of the treatment herein described may be readily appreciated by comparing it with the treatments heretofore known. The two types of treatment may be summarized:—The prior art treatment involves the administration of daily doses of 5—25 mg. of vitamin D, preferably daily doses of 5—10 mg. of vitamin D, continuously for months and years and shows results differing from investigator to investigator according to reported results including moderate, favourable, very favourable or even no therapeutic results and very often leads to toxic side effects dangerous to the life of the patient.

The novel treatment herein described involves the intermittent administration of even higher doses of about 40 to 100 mg. of vitamin D, a dosage which is repeated every 10 to 18 days and is well tolerated for prolonged periods in most cases substantially without side effects, showing extraordinarily favourable therapeutic results.

Since polyarthritis rheumatica chronica is a chronic disease in character it is reasonable for the treatment with vitamin D to be chronic, too, i.e. continued for months and years.

For the better understanding of the invention the following examples of suitable dosage unit compositions are given by way of illustration only:—

EXAMPLE 1.

6.000 kg. vitamin D-milk protein compound containing
1.2 kg. vitamin D_3
0.514 kg. vitamin B_1
1.028 kg. cholic acid
2.108 kg. lactose
0.350 kg. Indian corn starch
0.420 hardened gelatine
0.580 kg. talc
are mixed while excluding air in a mixing device. From this mixture tablets of 1.10 grams, a diameter of 18 mm. and a thickness of about 4.8 mm. are prepared. Each tablet contains 120 mg. of vitamin D_3.

EXAMPLE 2.

2.500 kg. vitamin D-milk protein compound containing
0.250 kg. vitamin D_2
0.107 kg. vitamin B_1
0.214 kg. cholic acid
0.219 kg. lactose
0.600 kg. mannitol
0.160 kg. potato starch
0.200 kg. talc
are mixed while excluding air in a mixing device. From this mixture tablets of 0.4 grams weight and a diameter of 12 mm. are prepared, each of which contains 25 mg. of vitamin D_2.

EXAMPLE 3.

12,000 kg. vitamin D-milk protein compound containing
0.600 kg. vitamin D_2
0.257 kg. vitamin B_1
0.514 kg. cholic acid
1.379 kg. lactose
3.200 kg. mannitol
0.620 kg. silicic acid gel
1.030 kg. talc
are mixed in a mixing device while excluding air. From this mixture tablets of 1.9 grams weight and a diameter of 22 mm. are prepared each of which contains 60 mg. of vitamin D_2.

EXAMPLE 4.

20.000 kg. vitamin D-milk protein compound containing
0.2 kg. vitamin D_3
0.086 kg. vitamin B_1
0.172 kg. cholic acid
1.802 kg. lactose
4.310 kg. mannitol
1.180 kg. hardened gelatine
1.450 kg. talc
are mixed, while excluding air, in a mixing device. From this mixture tablets of 2.9 grams weight and a diameter of 25 mm. are

prepared, each of which contains 20 mg. of vitamin D_3.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition for the treatment of rheumatic diseases which is in solid dosage unit form adapted for oral administration and which comprises vitamin D in association with a pharmaceutical carrier or excipient, each dosage unit containing from 20—150 mg. of vitamin D.

2. A composition as claimed in Claim 1 in the form of tablets or capsules.

3. A composition as claimed in Claim 1 or Claim 2 in which each dosage unit contains from 40—100 mg. of vitamin D.

4. A composition as claimed in any of the preceding claims in which each dosage unit contains from 60—80 mg. of vitamin D.

5. A composition as claimed in any of the preceding claims in which the vitamin D is vitamin D_2.

6. A composition as claimed in any of the preceding claims also comprising milk-protein.

7. A composition as claimed in Claim 6 in which the ratio of vitamin D to milk-protein is 1 : 3 to 1 : 150 by weight.

8. A composition as claimed in Claim 6 in which the ratio of vitamin D to milk-protein is 1 : 10 to 1 : 100 by weight.

9. A composition as claimed in any of the preceding claims also comprising vitamin B_1.

10. A composition as claimed in any of the preceding claims also comprising cholic acid.

11. A composition as claimed in any of the preceding claims comprising 3.5 parts by weight of vitamin D_2 and 0.5 to 10 parts by weight of vitamin B_1.

12. A composition as claimed in Claim 11, comprising also 1 to 10 parts by weight of cholic acid.

13. A composition as claimed in Claim 12, comprising 3.5 parts by weight of vitamin D_2, 1.5 parts by weight of vitamin B_1 and 3 parts by weight of cholic acid.

14. A composition as claimed in any one of Claims 1 to 13 wherein said excipient is starch, lactose, mannitol, hardened gelatine or talc.

15. Pharmaceutical compositions suitable for the treatment of rheumatic diseases substantially as herein described with reference to the examples.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15/19 Kingsway,
London, W.C.2.

Abingdon: Printed for Her Majesty's Stationery Office, by Burgess & Son (Abingdon), Ltd.—1964.
Published at The Patent Office, 25 Southampton Buildings, London, W.C.2,
from which copies may be obtained.